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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health

ACTION: Notice

SUMMARY: The invention listed below is owned by an agency of the U.S. Government and is available for licensing and/or co-development in the U.S. in accordance with 35 U.S.C. 209 and 37 CFR part 404 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing and/or co-development.

ADDRESS: Invention Development and Marketing Unit, Technology Transfer Center, National Cancer Institute, 9609 Medical Center Drive, Mail Stop 9702, Rockville, MD, 20850-9702.

FOR FURTHER INFORMATION, CONTACT: Information on licensing and co-development research collaborations, and copies of the U.S. patent applications listed below may be obtained by contacting: Attn. Invention Development and Marketing Unit, Technology Transfer Center, National Cancer Institute, 9609 Medical Center Drive, Mail Stop 9702, Rockville, MD, 20850-9702, Tel. 240-276-5515 or Email ncitechtransfer@mail.nih.gov. A signed Confidential Disclosure Agreement may be required to receive copies of the patent applications.

SUPPLEMENTARY INFORMATION: Technology description follows.

Title of invention: Immunotoxins with Increased Stability for Cancer Therapy

Keywords: Recombinant Immunotoxin, RIT, Antibody, Mesothelin, Mesothelioma

Description of Technology:

Recombinant immunotoxins (RITs) are fusions of an antibody-based targeting moiety and a toxin. Pseudomonas exotoxin A (PE) is a bacterial toxin that has been used in several RITs evaluated in clinical trials.[1,2] Once the Fv portion of the immunotoxin binds to its target receptor, the immunotoxin is internalized by endocytosis. Following internalization, Furin cleavage is critically important for proper cytosolic shuttling of the immunotoxin. Early PE-containing RITs were effective, but also had issues of off-target toxicity.

To mitigate off-target toxicity of PE, the inventors removed specific sequences of domain II, and connected the Fv domain to domain III (PE24) by a furin linker peptide. These PE24-RITs are very active and better tolerated by mice. However, the PE24-containing RITs could potentially be cleaved and inactivated before internalization by cell surface furin or other proteases in the bloodstream or the tumor microenvironment, due to the absence of a key disulfide bond (lost after removal of domain II sequences).

Researchers at the National Cancer Institute's Laboratory of Molecular Biology (NCI LMB) developed and isolated several de-immunized, low toxicity, PE24-based RITs with a longer serum half-life. This was enabled by using a disulfide bond to protect the furin cleavage sequence (FCS). Collectively, the new RITs are designated "DS-PE24" immunotoxins. The goal of the disulfide bond is to protect the RIT from cleavage-based deactivation before internalization. The most active of these new RITs has longer serum half-life than an RIT without the disulfide bond, has the same anti-tumor activity, while remaining less cytotoxic *in vitro*. Currently, the inventors are working with mouse models to further develop the DS-PE24 RITs towards developing an anti-mesothelin RIT

[1] Fitzgerald DJ, Kreitman R, et al. *Int J Med Microbiol.* 2004;293:577-582
[2] Sampson JH, Akabani G, Archer GE, et al. *J Neurooncol.* 2003;65(1):27-35

for treatment of mesothelin-expressing cancers, such as mesothelioma.

Potential Commercial Applications:

- A more stable cancer therapeutic for currently used PE-coupled RITs, for example, anti-mesothelin PE-based immunotoxins

Value Proposition:

- Protection of the FCS by a disulfide bond results in more stable RIT, which can lead to fewer off-target effects

Development Stage:
In-vivo

Inventor(s): Ira Pastan M.D. (NCI), *et al.*

Intellectual Property:
United States Provisional Patent Application 62/323,668 (NIH Reference E-157-2016/0-US-01), entitled "New, More Stable Immunotoxin Variants with a Disulfide Bond Protecting the Furin Cleavage Site"

Related Technologies

- NIH Reference E-262-2005, entitled "Mutated Pseudomonas Exotoxins with Reduced Antigenicity"
- NIH Reference E-292-2007, entitled "Deletions in Domain II of Pseudomonas Exotoxin A that Reduce Non-Specific Toxicity"
- NIH Reference E-174-2011, entitled "Pseudomonas Exotoxin A with Less Immunogenic T-Cell and/or B-Cell Epitopes"
- NIH Reference E-263-2011, entitled "Pseudomonas Exotoxin A with Less Immunogenic B-Cell Epitopes"

Collaboration Opportunity:

Researchers at the NCI seek parties interested in licensing DS-PE24 RITs

Contact Information:

Requests for copies of the patent application or inquiries about licensing, research collaborations, and co-development opportunities should be sent to John D. Hewes, Ph.D. email: john.hewes@nih.gov

Dated: September 5, 2016

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[FR Doc. 2016-21906 Filed: 9/12/2016 8:45 am; Publication Date: 9/13/2016]